IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	Docket No.: **TI-28441B**
Anand G. Dabak	Art Unit: **2631**
Serial No.: **10/659,906**	Examiner: **Corrielus, Jean**
Filed: **09/11/03**	Conf. No.: **TBD**

For: **SPACE TIME BLOCK CODED TRANSMIT ANTENNA DIVERSITY FOR WCDMA**

PRELIMINARY AMENDMENT

Commissioner for Patents
Alexandria, VA 22313-1450

MAILING CERTIFICATE UNDER 37 CFR § 1.8(a)

I hereby certify that on this date, this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner For Patents and Trademarks, Alexandria, VA 22313-1450.

Elizabeth Austin 10/7/2003

Dear Sir:

This Preliminary Amendment is in addition to the Preliminary Amendment of June 23, 2003. Please enter this amendment prior to examination of the above-identified application:

Amendments to the Claims begin on page 2 of this paper.

Remarks/Arguments begin on page 9 of this paper.

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re Application of **Anand G. Dabak**
Serial No.: **10/659,906**
Filed: **09/11/2003**
For: **Space Time Block Coded Transmit Antenna Diversity for WCDMA**

Docket No.: **TI-28441B**
Examiner: **Corrielus, Jean**
Art Unit: **2631**
Conf. No.: **TBD**

AMENDMENT TRANSMITTAL FORM

MAILING CERTIFICATE UNDER 37 C.F.R. § 1.8(a)

I hereby certify that on this date, this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Alexandria, VA 22313-1450 on October 7, 2003.

Elizabeth Austin

Commissioner for Patents
Alexandria, VA 22313-1450

Sir:

Transmitted herewith is an amendment in the above-identified application.

The fee has been calculated as shown below:

CLAIMS AS AMENDED						
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	ADDITIONAL FEE
Total Claims	43	Minus	20	23	x $18 =	$414.00
Independent Claims	4	Minus	3	1	x $86 =	$ 86.00
					TOTAL ADDITIONAL FEE	$500.00

Charge the total additional fee, and any further fees, or credit overpayment to the deposit account of Texas Instruments Incorporated, Account No. 20-0668. An original and two copies of this sheet are enclosed.

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AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application.

LISTING OF CLAIMS:

23. (Currently Amended) A mobile communication system, comprising:

a mobile antenna arranged to receive a plurality of signals from multiple signal paths from each of plural remote antennas of an external source;

an input circuit coupled to receive the plurality of signals from the mobile antenna, the input circuit producing a plurality of input signals including a first input signal ~~from a first remote antenna~~ and a second input signal ~~from a second remote antenna~~, at least one of the first and at least one of the second input signals corresponding to the same datum; and

a correction circuit coupled to receive a plurality of ~~first~~ estimate signals~~, a second estimate signal~~ and the first and second input signals, the plurality of ~~first~~ estimate signals corresponding to respective signal paths ~~of the first input signal~~, the correction circuit producing a first symbol estimate and a second symbol estimate in response to the ~~first and second~~ estimate signals and the first and second input signals.

24. (Previously presented) A mobile communication system as in claim 23, further comprising a combining circuit coupled to receive a plurality of first symbol estimates including the first symbol estimate and coupled to receive a plurality of second symbol estimates including the second symbol estimate, the combining circuit producing a first symbol signal in response to the plurality of first symbol estimates and producing a second symbol signal in response to the plurality of second symbol estimates.

25. (Previously presented) A mobile communication system as in claim 24, wherein the input circuit, the correction circuit and the combining circuit are formed on a single integrated circuit.

26. (Previously presented) A mobile communication system as in claim 24, wherein each of the first and second symbol signals include at least one of a pilot symbol, a transmit power control symbol, a rate information symbol and a data symbol.

27. (Previously presented) A mobile communication system as in claim 23, wherein each of the first and second estimate signals include at least one of a pilot symbol, a transmit power control symbol, a rate information symbol and a data symbol.

28. (Previously presented) A mobile communication system as in claim 23, wherein a total diversity of each of the first and second symbol signals is at least twice a number of the plural remote antennas.

29. (Previously presented) A mobile communication system as in claim 23, wherein each of the first and second input signals is a wideband code division multiple access signal.

30. (Previously presented) A mobile communication system as in claim 29, wherein a total diversity of each of the first and second symbol signals is at least twice a number of the plural remote antennas.

31. (Previously presented) A mobile communication system as in claim 23, wherein the mobile antenna receives the first and second input signals over a common channel.

32. (Previously presented) A mobile communication system as in claim 23, wherein the mobile antenna receives the first and second input signals over a common frequency band.

33. (Previously presented) A mobile communication system as in claim 23, wherein the first input signal comprises a data symbol and the second input signal comprises a complex conjugate of the data symbol.

34. (New) An apparatus, comprising:

a correction circuit coupled to receive a first transmitted symbol from a first antenna at a first time and a conjugate of a second transmitted symbol from a second antenna at the first time, the correction circuit producing a first symbol estimate in response to a first received symbol and the conjugate of a second received symbol; and

a combining circuit coupled to receive a plurality of symbol estimates including the first symbol estimate, the plurality of symbol estimates corresponding to a respective plurality of signal paths, the combining circuit producing a first symbol in response to the plurality of symbol estimates.

35. (New) An apparatus as in claim 34, wherein the correction circuit is further coupled to receive the second symbol from the first antenna at a second time and a complement of a conjugate of the first symbol from the second antenna at the second time.

36. (New) An apparatus as in claim 35, wherein the correction circuit produces the first symbol estimate and a second symbol estimate in response to the first transmitted symbol, the conjugate of the second transmitted symbol, a second transmitted symbol, and the complement of a conjugate of the first transmitted symbol.

37. (New) An apparatus as in claim 36, wherein the correction circuit is further coupled to receive a first estimate signal and a second estimate signal and wherein the correction circuit produces the first symbol estimate and the second symbol estimate in response to the first transmitted symbol, the conjugate of the second transmitted symbol, the second transmitted symbol, the complement of the conjugate of the first transmitted symbol, the first estimate signal, and the second estimate signal.

38. (New) An apparatus as in claim 34, wherein the correction circuit receives the first symbol and the conjugate of the second symbol over a common channel.

39. (New) An apparatus as in claim 34, wherein the correction circuit receives the first symbol and the conjugate of the second symbol over a common frequency band.

40. (New) An apparatus as in claim 34, wherein the plurality of symbol estimates corresponds to one of the first and second symbols.

41. (New) An apparatus as in claim 34, wherein the combining circuit is a rake combiner.

42. (New) A method of processing signals in a communication circuit, comprising the steps of:

receiving a first transmitted symbol from a first antenna at a first time and a conjugate of a second transmitted symbol from a second antenna at the first time;

producing a first symbol estimate in response to a first received symbol and a conjugate of a second received symbol;

receiving a plurality of symbol estimates including the first symbol estimate, the plurality of symbol estimates corresponding to a respective plurality of signal paths; and

producing a first symbol in response to the plurality of symbol estimates.

43. (New) The method of claim 42, further comprising the step of receiving the second symbol from the first antenna at a second time and a complement of a conjugate of the first symbol from the second antenna at the second time.

44. (New) The method of claim 43, further comprising the step of producing the first symbol estimate and a second symbol estimate in response to the first symbol, the conjugate of the second symbol, the second symbol, and the complement of the conjugate of the first symbol.

45. (New) The method of claim 43, further comprising the step of receiving a first estimate signal and a second estimate signal and producing the first symbol estimate and the second symbol estimate in response to the first symbol, the conjugate of the second symbol, the second symbol, the complement of the conjugate of the first symbol, the first estimate signal, and the second estimate signal.

46. (New) The method of claim 42, wherein the first symbol and the conjugate of the second symbol are received over a common channel.

47. (New) The method of claim 42, wherein the first symbol and the conjugate of the second symbol are received over a common frequency band.

48. (New) The method of claim 42, wherein the plurality of symbol estimates corresponds to one of the first and second symbols.

49. (New) The method of claim 42, wherein the combining circuit is a rake combiner.

50. (New) An apparatus, comprising:

a correction circuit coupled to receive a first symbol comprising one symbol transmitted from a first antenna at a first time and a conjugate of another symbol transmitted from a second antenna at the first time, the correction circuit producing a first symbol estimate in response to the first symbol and the conjugate of a second symbol; and

a combining circuit coupled to receive a plurality of symbol estimates including the first symbol estimate, the plurality of symbol estimates corresponding to a respective plurality of signal paths, the combining circuit producing a combined symbol in response to the plurality of symbol estimates.

51. (New) An apparatus as in claim 50, wherein the correction circuit is further coupled to receive the second symbol from the first antenna at a second time and a complement of a conjugate of the first symbol from the second antenna at the second time.

52. (New) An apparatus as in claim 51, wherein the correction circuit produces the first symbol estimate and a second symbol estimate in response to receiving said one symbol, said conjugate of said another symbol, yet another symbol, and a complement of a conjugate of said one symbol.

53. (New) An apparatus as in claim 50, wherein the correction circuit is further coupled to receive a first estimate signal and a second estimate signal and wherein the correction circuit produces the first symbol estimate and the second symbol estimate in response to said one symbol, the conjugate of the second transmitted symbol, said another symbol, the complement of the conjugate of said one symbol, the first estimate signal, and the second estimate signal.

54. (New) An apparatus as in claim 50, wherein the correction circuit receives the first symbol and the conjugate of the second symbol over a common channel.

55. (New) An apparatus as in claim 50, wherein the correction circuit receives the first symbol and the conjugate of the second symbol over a common frequency band.

56. (New) An apparatus as in claim 50, wherein the plurality of symbol estimates corresponds to one of the first and second symbols.

57. (New) An apparatus as in claim 50, wherein the combining circuit is a rake combiner.

58. (New) A method of processing signals in a communication circuit, comprising the steps of:

receiving a first symbol comprising a symbol from a first antenna at a first time and a conjugate of another symbol from a second antenna at the first time;

producing a first symbol estimate in response to the first symbol and a conjugate of a second symbol;

receiving a plurality of symbol estimates including the first symbol estimate, the plurality of symbol estimates corresponding to a respective plurality of signal paths; and

producing a combined symbol in response to the plurality of symbol estimates.

59. (New) The method of claim 58, further comprising the step of receiving the second symbol from the first antenna at a second time and a complement of a conjugate of the first symbol from the second antenna at the second time.

60. (New) The method of claim 59, further comprising the step of producing the first symbol estimate and a second symbol estimate in response to the first symbol, the conjugate of the second symbol, the second symbol, and the complement of the conjugate of the first symbol.

61. (New) The method of claim 59, further comprising the step of receiving a first estimate signal and a second estimate signal and producing the first symbol estimate and the second symbol estimate in response to the first symbol, the conjugate of the second symbol, the second symbol, the complement of the conjugate of the first symbol, the first estimate signal, and the second estimate signal.

62. (New) The method of claim 58, wherein the first symbol and the conjugate of the second symbol are received over a common channel.

63. (New) The method of claim 58, wherein the first symbol and the conjugate of the second symbol are received over a common frequency band.

64. (New) The method of claim 58, wherein the plurality of symbol estimates corresponds to one of the first and second symbols.

65. (New) The method of claim 58, wherein the combining circuit is a rake combiner.

REMARKS/ARGUMENTS

Claim 23, added in the Preliminary Amendment of June 23, 2003, has been amended. New Claims 34-65 have been added. Claims 23-65 stand allowable over the cited art and the application is in allowable form. Applicants respectfully request allowance of the application as the earliest possible date.

Independent Claim 23, as amended, requires and positively recites, a mobile communication system, comprising: "a mobile antenna arranged to receive a plurality of signals **from multiple signal paths from each of plural remote antennas** of an external source", "an input circuit coupled to receive the plurality of signals from the mobile antenna, the input circuit producing a plurality of input signals including a first input signal and a second input signal, at least one of the first and at least one of the second input signals corresponding to the same datum" and "a correction circuit coupled to receive a plurality of estimate signals and the first and second input signals, the plurality of estimate signals corresponding to respective signal paths, the correction circuit producing a first symbol estimate and a second symbol estimate in response to the estimate signals and the first and second input signals".

In contrast, the Alamouti reference discloses an apparatus in which there is a SINGLE signal path from each of plural remote antennas 31 and 32 to remote antenna 51 since the disclosure is limited to time division multiple access (TDMA). As a result, Alamouti fails to disclose multiple signal paths between a transmit antenna 31 OR 32 and a receive antenna 51 or 52.

In order that the rejection of any of Claims 23-33 be sustainable, it is fundamental that "each and every element as set forth in the claim be found, either expressly or inherently described, in a single prior art reference." Verdegall Bros. v.

Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). See also, Richardson v. Suzuki Motor Co., 9 USPQ2d 1913, 1920 (Fed. Cir. 1989), where the court states, "The identical invention must be shown in as complete detail as is contained in the ... claim".

Furthermore, "all words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

From the discussion above, it is apparent that independent Claim 23, as amended, is not anticipated by Alamouti. Moreover, the Examiner has provided no evidence from the prior art that would lead one having ordinary skill in the art to re-engineer the Alamouti device to have multiple signal paths between a transmit antenna 31 or 32 and a receive antenna 51 or 52, without the improper hindsight provided by Applicant's disclosure

Claims 24, 26-28, 29, 30 and 31-33 stand allowable as depending, directly or indirectly, from allowable Claim 23 and including further limitations not taught or suggested by the references of record.

Dependent Claim 24 requires and positively recites, a mobile communication system as in claim 23, further comprising a combining circuit coupled to receive a plurality of first symbol estimates including the first symbol estimate and coupled to receive a plurality of second symbol estimates including the second symbol estimate, the combining circuit producing a first symbol signal in response to the plurality of first symbol estimates and producing a second symbol signal in response to the plurality of second symbol estimates. Alamouti fails to teach or suggest this additional limitation in combination with the other requirements of Claim 23.

Dependent Claim 25 requires and positively recites a mobile communication system as in claim 24, wherein the input circuit, the correction circuit and the combining circuit are formed on a single integrated circuit. Alamouti fails to teach or suggest this additional limitation in combination with the other requirements of Claim 24.

Dependent Claim 26 requires and positively recites a mobile communication system as in claim 24, wherein each of the first and second symbol signals include at least one of a pilot symbol, a transmit power control symbol, a rate information symbol and a data symbol. Being that Alamouti discloses a TDMA system, it fails to teach or suggest this additional limitation in combination with the other requirements of Claim 24.

Dependent Claim 27 requires and positively recites a mobile communication system as in claim 23, wherein each of the first and second estimate signals is a Rayleigh fading parameter estimate. Alamouti fails to teach or suggest this additional limitation in combination with the other requirements of Claim 23.

Dependent Claim 28 requires and positively recites a mobile communication system as in claim 23, wherein a total diversity of each of the first and second symbol signals is at least twice a number of the plural remote antennas. Alamouti fails to teach or suggest this additional limitation in combination with the other requirements of Claim 23.

Dependent Claim 29 requires and positively recites a mobile communication system as in claim 23, wherein each of the first and second input signals is a wideband code division multiple access signal. Being that Alamouti discloses TDMA transmission, Alamouti fails to teach or suggest this additional limitation in combination with the other requirements of Claim 23.

Dependent Claim 30 requires and positively recites a mobile communication system as in claim 29, wherein a total diversity of each of the first and second symbol signals is at least twice a number of the plural remote antennas. Alamouti fails to teach or suggest this additional limitation in combination with the other requirements of Claim 29.

Dependent Claim 31 requires and positively recites a mobile communication system as in claim 23, wherein the mobile antenna receives the first and second input signals over a common channel. Alamouti fails to teach or suggest this additional limitation in combination with the other requirements of Claim 23.

Dependent Claim 32 requires and positively recites a mobile communication system as in claim 23, wherein the mobile antenna receives the first and second input signals over a common frequency band. Alamouti fails to teach or suggest this additional limitation in combination with the other requirements of Claim 23.

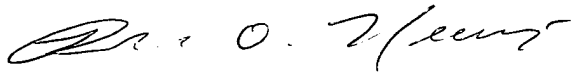
Dependent Claim 33 requires and positively recites a mobile communication system as in claim 23, wherein the first input signal comprises a data symbol and the second input signal comprises a complex conjugate of the data symbol. Alamouti fails to teach or suggest this additional limitation in combination with the other requirements of Claim 23.

Claim 23, as amended, clearly confirms Applicant's statement in the amendment dated 9/26/02 in parent application 09/205,029, that Alamouti does not disclose multiple signal paths between a transmit antenna and a receive antenna (page 4, lines 22-23) – whereas the present invention does.

New Claims 34-65 are similarly allowable over the references of record.

Claims 23-65 stand allowable over the cited art and the application is in allowable form. Applicants respectfully request allowance of the application as the earliest possible date.

Respectfully submitted,



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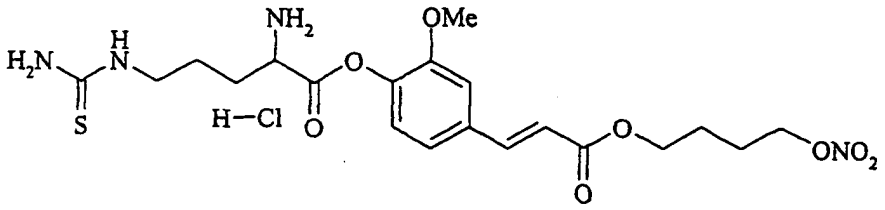
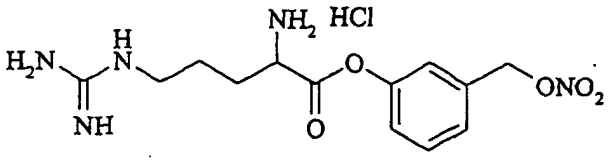
alpha-amino-delta-thioureidopentanoic acid, 2-methoxy-4-[(1E) -3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXIII)



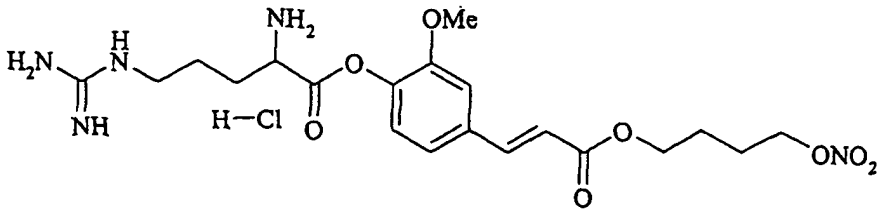
(XXIII)

2-amino-5-guanidinopentanoic acid, 3-(nitrooxy methyl)phenyl hydrochloride ester (XXIV)



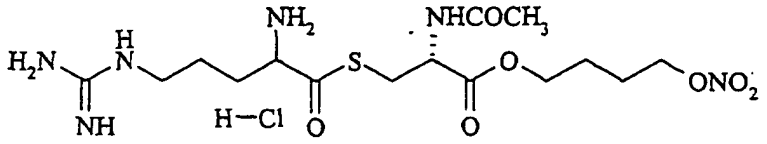
(XXIV)

2-amino-5-guanidinopentanoic acid-, 2-methoxy-4-[(1E)- 3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXV)



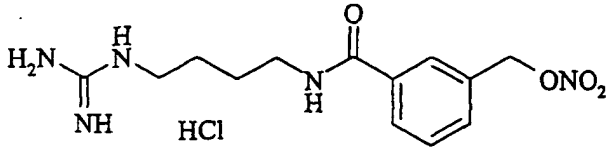
(XXV)

(S)-N-acetylcysteine-4-(nitrooxy)butyl ester, 2-amino-5-guanidinopentanoate hydrochloride (XXVI)



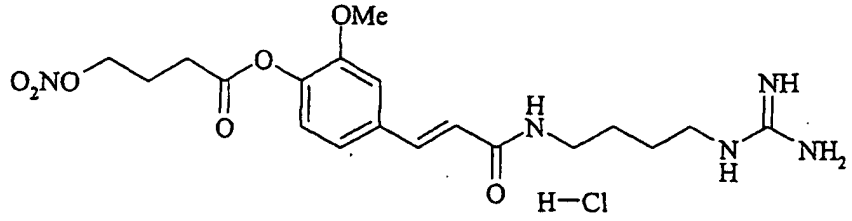
(XXVI)

4-(guanidine)butyl-3-nitrooxymethylbenzamide (XXVII)



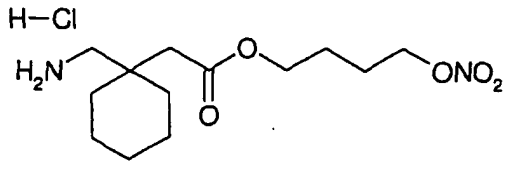
(XXVII)

4-(guanidine)butyl-3-[4-(4'-nitrooxybutyryloxy)-3-(methoxy)]phenyl-2-propenamide chloride (XXVIII)



(XXVIII)

1-(aminomethyl)cyclohexan acetic acid 4-(nitroxy)butyl hydrochloride ester (XXIX)



(XXIX)

The preferred above mentioned compounds with the formulas (XV)- (XXIX) can be used as nitrate salts.

The compounds according to the present invention, when they contain in the molecule one salifiable nitrogen atom, can be transformed into the corresponding salts by reaction in organic solvent such as for example acetonitrile, tetrahydrofuran with an equimolar amount of the corresponding organic or inorganic acid.

Examples of organic acids are: oxalic, tartaric, maleic, succinic, citric acid.

Examples of inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acid.

Salts with nitric acid are preferred.

The compounds of the invention have shown to have an improved activity with respect to the precursor drugs in the epilepsy treatment.

To evaluate the efficacy in the epilepsy treatment of the compounds of the present invention, one of the following pharmacological tests were used.

I) Limbic convulsions induced by pilocarpine (De Sarro G.B. et al. Eur. J. Pharmacol. 349: 179-185, De Sarro G.B., Brain Res. 591: 209-222, Turski W.A., Behav. Brain Res., 9: 315-336).

Male Sprague-Dawley rats weighing 280-350 g were used; they were subcutaneously injected with 1 mg/Kg of scopolamine. 15 minutes later, to the groups of animals the tested nitrooxyderivatives and the corresponding precursor drugs, dissolved in sterile saline solution were respectively administered by intraperitoneal injection. After one hour from the scopolamine injection, pilocarpine hydrochloride,

dissolved in saline solution, was administered by intraperitoneal injection at the doses of 200 or 350 mg/kg.

At the end of the treatments the animals were placed in circular Plexiglass cages (40 cm diameter.) For a time of 180 minutes after the administration of pilocarpine hydrochloride, the onset time and the intensity of the convulsions were checked.

The response of each animal was rated on the basis of a score assigned according to the scheme:

0 no reaction

1 perioral movements and scratching

2 tremors and relaxation of the hind paws

3 head movements and/or animal walking backwards

4 animal rising on the hind paws and tremors of the fore paws

5 falls

6 diffused tremors in the whole body

7 tonic clonic convulsions.

Method by analysis of the electroencephalographic tracing.

In this experiment were used mice belonging to a lethargic mice stock (Lh/Lh) which, when aged of about 15 days develop an ataxic behaviour (Hosford DA Adv Neurol. 1999; 79: 239-252).

The animals, between 11 and 17 weeks old, were anaesthetized with ketamine (7.5 mg/g, i.p.) and medetomidine (0.1 mg/100 g, i.p.). In the frontal cortex and in the parietal cortex (0.8 mm under the dura mater) of each animal two microelectrodes connected to an apparatus for recording the electroencephalographic trace and to a cannula for administering the compounds were inserted.

Once a week, counted by the insertion of the electrodes, an electroencephalographic trace of 2 hours was recorded.

After 15 minutes from the registration of the basic tracing, to the groups of mice solutions of the compounds, the corresponding precursor drugs in sodic phosphate buffer (67 mM) and the carrier were respectively administered by intracerebral infusion (2.5 µl/min for a total volume of 10 µl).

After the pharmacological treatment the electroencephalographic tracing was recorded for 3 hours and the animals were kept under observation for checking behaviour changes.

Absences were quantified on the basis of the duration of the spike discharges on the electroencephalogram as described by Hosford DA et al. Science, 1992 Jul 17; 257(5068): 398-401 (variations of the electroencephalographic trace of amplitudes not lower than 60 µV and of frequencies in the range 5-6 Hz were recorded, attacks must last not less than 0.6 sec).

The electroencephalographic tracing were recorded by amplification of 200-300 µV/cm and with a paper speed of 3 mm/sec.

In order to test the pharmacological effect of the compounds, each electroencephalographic tracing of 3 hours was divided into sections of 30 minutes and for each section the total duration of the spike and wave discharges was calculated; it was then normalized dividing this value by the corresponding value obtained after the administration of the vehicle.

II) Evaluation of anticonvulsant activity in DBA/2 mice after auditory stimulation

Groups of DBA/2 mice (weight 6 to 12 g, 22-26 days old) were treated with testing compounds. All compounds were given intraperitoneally (i.p.) dissolved in sterile saline solution 60 min prior of exposing mice to auditory stimulation. For each dose of compounds studied against audiogenic seizure 10 mice were used.

Each mouse was placed under a hemispheric perspex dome (diameter 58 cm) and left for 1 min in order to allow habituation and assessment of locomotor activity. Auditory stimulation (12-16 kHz, 109 dB) was applied for 1 min or until tonic extension occurred. Seizure response was assessed according to De Sarro GB et al. Neuropharmacology, 23(5):525-30, 1984) using the following scale: 0 = no response, 1 = wild running, 2 = clonus, 3 = tonus, 4 = respiratory arrest. The maximum response was recorded for each animal. Rectal temperature was recorded immediately prior to auditory testing using an Elektrolaboratoriet thermometer type T.E.3. Behavioural changes were monitored during period between drug administration and auditory testing.

III) Evaluation of anticonvulsant activity by convulsant agent pentylenetetrazole

Groups of ICR CD1 mice (weight 16 to 24 g, 42 to 48 days old) were treated with testing compounds to evaluate the pharmacological effects on subconvulsant (40 mg/kg) or convulsant (CD_{97}, 85 mg/kg) dose of pentylenetetrazole was used. All compounds were administered intraperitoneally (i.p.), as above indicated, 60 min before a subcutaneous (s.c.) injection

of pentylenetetrazole (0.1 ml/10 g of body weight). All ICR CD1 mice were observed for 60 min. Animals were scored as seizure positive if they exhibited continuous limb clonus lasting 3 s or of longer duration. For each dose of compounds studied against pentylenetetrazole seizure 10 mice were used.

The compounds of the invention can also be used in combination with NO-donor compounds of the prior art.

The NO donor compounds which can be used in combination with the invention compounds must comply with the test in vitro defined hereinafter.

The test relates to the generation of nitric oxide from the NO donors, for example nitroglycerin, niocorandil, nitroprussiate, etc., in the presence of endothelial cells (method a) or platelets (method b).

a) Endothelial cells

Cells of the human umbilical vein, cultured on plates, having a 10^3 density cells/well were incubated for 5 minutes with scalar concentrations of NO donor (1-100 µg/ml). The incubation medium (physiologic solution, for example Tyrode) was then analyzed to determine the capability to generate NO of the compound under test, by means of:

1) nitric oxide detection by chemiluminescence;
2) cGMP determination (cyclic GMP n° 2715 of the above mentioned Merck).

For the analysis by chemiluminescence, an amount equal to 100 µl was injected in the reaction chamber of a chemiluminescence analyzer containing glacial acetic acid and potassium iodide. The nitrites/nitrates present in the medium, under these conditions, are converted into NO

which is then detected after reaction with ozone, which produces light. In the equipments measuring the chemiluminescence, the produced luminescence is directly proportional to the generated NO levels and can be measured by a suitable photomultiplying unit of a chemiluminescence analyzer. The photomultiplier converts the incident light into electric voltage, which is quantitatively recorded. On the basis of a calibration curve, prepared with scalar nitrite concentrations, it can be quantitatively determined the generated NO concentration. For example, from the incubation of 100 µM of nicorandil, an amount equal to about 10 µM of NO was generated.

For cGMP determination, an aliquot of the incubation medium (equal to 100 µl) was centrifuged at 1,000 revolutions for 20 seconds. The surnatant was removed and the sediment treated with iced phosphate buffer (pH 7.4). The produced cGMP levels were tested by specific immunoenzymatic reactants. From said experiments it resulted that, under these experimental conditions, the incubation with one of the various tested NO donors caused a significant increase of cGMP with respect to the values obtained in absence of a NO donor. For example, after incubation with 100 µM of sodium nitroprussiate, an increase of about 20 times the value obtained with the incubation of the carrier alone, without NO donor was recorded.

b) Platelets

Washed human platelets, prepared substantially in the same way as described by Radomski et al, (Br. J.

Pharmacol. 92, 639-1987), were used. Aliquots of 0.4 ml were incubated for 5 minutes with NO-donor scalar concentrations (1-100 µg/ml). The incubation medium (for ex. Tyrode) was then analyzed to determine the capability of the tested compound to generate NO, by the determination of nitric oxide by chemiluminescence and the determination of cGMP, as described in the previous paragraph for the same analyses carried out on the endothelial cells. For the determination by chemiluminescence, also in this case, on the basis of a calibration curve prepared with scalar concentrations of nitrite, it was possible to quantitatively determine the produced NO amount. For example, after incubation of 100 µM of nicorandil, an amount equal to 35 µM of NO was generated.

For cGMP determination, it resulted that also under these experimental conditions the incubation with one of the tested NO donors gave a significant increase of cGMP with respect to the values obtained in absence of a NO donor. For example, after incubation with 100 µM of sodium nitroprussiate, an increase of about 30 times the value obtaind with the incubation of the only carrier without NO donor took place.

The preferred NO-donor compounds are those which in the molecule contain radicals of drugs belonging to the classes of aspirin, ibuprofen, paracetamol, naproxen, diclofenac, flurbiprofen and are described in patent applications WO 95/20641, WO 97/16405, WO 95/09831, WO 01/12584.

The compounds of the present invention can be synthesized as follows.

Generally when in the drug molecule more reactive groups such as for example COOH and/or HX are present, they must be protected before the reaction according to the methods known in the prior art; for examaple as described in the volume by Th. W. Greene: "Protective groups in organic synthesis", Harward University Press, 1980.

The acylhalides are prepared according to the methods known in the prior art, for example by thionyl or oxalyl chloride, halides of P^{III} or P^{V} in solvents inert under the reaction conditions, such as for example toluene, chloroform, DMF, etc.

1) When in formula (I) b0 = 0 and the free valence of the radical R of the drug is saturated with a carboxylic group, the synthesis methods to obtain the corresponding nitrooxyderivatives are the following:

1.A) The drug of formula RCOOH is treated with an agent activating the carboxyl group selected from N,N'carbonyldiimidazol (CDI), N-hydroxybenzotriazol and dicyclohexylcarbodiimide (DCC) in solvent such as for example DMF, THF, chloroform, etc., at a temperature in the range from -5°C to 50°C and reacted in situ with a compound HO-Y-Hal, wherein Y and Hal are as above defined.

$$RCOOH \xrightarrow{DCC,\ HO\text{-}Y\text{-}Hal} R\text{-}CO\text{-}O\text{-}Y\text{-}Hal \qquad (1C)$$

1.B) Alternatively, the drug acylhalide is reacted with a compound $HO\text{-}Y\text{-}R_{8A}$, wherein Y is as above, R_{8A} is OH or halogen in the presence of a base, in an organic solvent inert under the reaction conditions according to the scheme below reported:

$$RCOHal + HO\text{-}Y\text{-}R_{8A} \dashrightarrow R\text{-}COO\text{-}Y\text{-}R_{8A} \quad (1D)$$

1.C) When the compounds obtained in the above reactions have formula R-COO-Y-Hal the corresponding nitrooxyderivatives are obtained by reacting the compound R-CO-O-Y-Hal with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran according to the scheme:

$$R\text{-}COO\text{-}Y\text{-}Hal + AgNO_3 \longrightarrow R\text{-}COO\text{-}Y\text{-}ONO_2$$

1.D) When the compounds obtained in the above reactions have formula R-COO-Y-OH the hydroxyl group is subjected to halogenation, for example with PBr_3, PCl_5, $SOCl_2$, PPh_3 + I_2, and then reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran.

2) When in formula (I) b0 = 0, and the reactive function of the drug is the group NH_2, the synthesis methods to obtain the corresponding nitrooxyderivatives are the following:

2.a) By reaction of the drug $R\text{-}NH_2$ with an acyl halide of formula Hal-Y-COHal, wherein Y and Hal are as above, according to the scheme:

$$R\text{-}NH_2 + Hal\text{-}Y\text{-}COHal \longrightarrow R\text{-}NHCO\text{-}Y\text{-}Hal \quad (2A)$$

2.b) By reaction of the drug $R\text{-}NH_2$ with an acyl halide of formula OH-Y-COHal, wherein Y and Hal are as above, according to the scheme:

$$R\text{-}NH_2 + Hal\text{-}Y\text{-}COCl \longrightarrow R\text{-}NHCO\text{-}Y\text{-}OH \quad (2B)$$

2.c) When the compounds obtained in the above reactions have formula R-NHCO-Y-Hal or R-NHCO-Y-OH the corresponding nitrooxyderivatives are obtained as above described in 1.C and 1.D respectively.

3. When in formula (I) b0 = c0 = 1, and the free valence of the radical R of the drug is saturated with a carboxylic

group, the synthesis methods to obtain the corresponding nitrooxyderivatives are the following:

3.a) Alternatively the acyl halide of the drug and the compound of formula $HX-X_2-COOH$, wherein X and X_2 are as above, are reacted according to the methods known in the prior art, to give the compound $R-CO-X-X_2-COOH$ which is transformed into the corresponding sodic salt and reacted with a compound of formula $Hal-Y-R_8$ wherein Hal and Y are as above and R_8 is Cl, Br, Iodine, OH:

$$R-COHal + HX-X_2-COOH \dashrightarrow R-CO-X-X_2-COOH \quad (3.A)$$

$$R-CO-X-X_2-COONa + Hal-Y-R_{8A} \dashrightarrow R-CO-X-X_2-CO-Y-R_{8A} \quad (3.A')$$

When R_{8A} = OH the compound of formula (3.A') is subjected to halogenation as above described in 1.D, when R_{8A} = Hal the compound of formula (3.A') is reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran.

3.b) When Y_T is a C_4 linear alkylene, the precursor of B of formula $HO-X_2-COOH$ is reacted with triphenylphosphine in the presence of a halogenating agent such as CBr_4 or N-bromosucciniimide in tetrahydrofuran to give the compound of formula $HO-X_2-COO(CH_2)_4Br$ which is reacted with the molecule of the drug RCOOH as described in 1.A and 1.C.

4) When in formula (I) p = 1 b0 = c0 = 1, and the reactive function of the drug is the group NH_2, the synthesis methods to obtain the corresponding nitrooxyderivatives are the following:

4.a) Reaction of the drug $R-NH_2$ with an acyl halide of formula $HX-X_2-COHal$, wherein X and X_2 are as above, according to the methods known in the prior art, to give the compound $R-NH-CO-X_2-XH$ which is reacted with a compound of formula $R_{8A}-Y-COHal$ wherein R_{8A} and Y are as above.

$R-NH_2 + HX-X_2-COCl \dashrightarrow R-NH-CO-X_2-XH$ (4.A)

$R-NH-CO-X_2-XH + R_{8A}-YCO-Hal \dashrightarrow R-NH-CO-X_2-X-CO-Y-R_{8A}$ (4A')

4.b) Alternatively, the drug $R-NH_2$ is reacted with a compound of formula $HX-X_2-COOH$, wherein X and X_2 are as above, in the presence of dicyclohexylcarbodiimide as described in 1.A, to give the compound $R-NH-CO-X_2-XH$, which is reacted with a compound of formula $R_{8A}-Y-COCl$ wherein R_{8A} and Y are as above defined, to give the following compound: $R-NH-CO-X_2-X-CO-Y-R_{8A}$ (4.B)

When R_{8A} = OH the compound of formula (4.B) or of formula (4a') is subjected to halogenation as above described in 1.D; when R_{8A} = Hal the compound of formula (4.B) is reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran.

When the compounds in the present invention have one or more chiral centres, they can be in racemic form or as mixtures of diastereoisomers, enantiomers, as single enantiomers or single diastereoisomers; when the compound shows a geometric asymmetry the compounds in the cis or trans form can be used.

The compounds of the present invention are formulated in the corresponding pharmaceutical compositions for parenteral, oral use, etc., according to the tchniques well known in the field, together with the usual excipients; see for example the volume "Remington's Pharmaceutical Sciences 15th Ed."

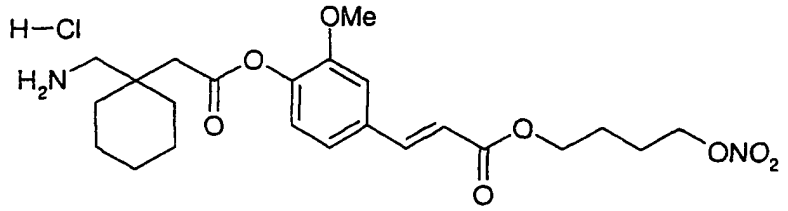
The amount on a molar basis of the active principle in said formulations is equal to or lower than the maximum posology indicated for the precursor drugs. Also higher doses can be used, considering their very good tolerability.

The administrable daily doses are those of the precursor drugs, or even lower. The daily doses can be found in the publications of the field, such as for example in "Physician's Desk reference".

The following Examples illustrate the invention without limiting the scope thereof.

EXAMPLE 1

Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl] phenyl hydrochloride ester (XV)



A) Synthesis of the 1-(N-tert-butoxycarbonylaminomethyl) cyclohexan acetic acid

To a solution of 1-(aminomethyl)cyclohexanacetic acid (10 g, 58.4 mmoles) in a mixture of dioxane (100 ml) and water (150 ml), triethylamine (16.27 ml, 116.8 mmoles) and di-tert-butyldicarbonate (15.3 g, 70 mmoles) are added. The reaction mixture is left at room temperature, under stirring for 4 hours. After having cooled the solution to 0°C it is brought to pH 2 with HCl 5%. The precipitate is filtered and dried under vacuum. 15 g of the expected compound are obtained as a white solid having m.p. = 125°-127°C.

B) Synthesis of 2-methoxy-4-[(1E)-3-[4-(bromo)butoxy]-3-oxy-1-propenyl]phenol

To a solution of ferulic acid (11.6 g, 59.7 mmoles) in tetrahydrofuran (400 ml), tetrabromomethane (39.62 g, 119.47

mmoles) and triphenylphosphine (31.34 g, 119.47 mmoles) are added. The obtained mixture is kept under stirring at room temperature for 5 hours, filtered and evaporated at reduced pressure. The residual crude compound is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 8 g of the expected compound are obtained as a yellow solid having m.p. = 86°-89°C.

C) Syntheis of 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-*propenyl*]*phenol*

To a solution of 2-methoxy-4-[(1E)-3-[4-(bromo) butoxy]-3-oxy-1-propenyl]phenol (8 g, 24.3 mmoles) in acetonitrile (500 ml) silver nitrate (12.25 g, 72.9 mmoles) is added. The reaction mixture is heated at 40°C for 12 hours sheltered from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 75/25. 4 g of the expected compound are obtained as a yellow solid having m.p. = 65°-68°C.

D) Synthesis of the 1-(N-tert-butoxycarbonylaminomethyl) cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl ester

To a solution of 1-(N-tert-butoxycarbonyl aminomethyl) cyclohexan acetic acid (2.5 g, 9.2 mmoles) in chloroform (200 ml) and N,N-dimethylformamide (3 ml), 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl] phenol (3.15 g, 10.1 mmoles), dicyclohexylcarbodiimide (5.7 g, 27.6 mmoles) and N,N-dimethylaminopyridine (33 mg, 0.27 mmoles) are added.

The reaction mixture is left at room temperature, under stirring for 3 hours, filtered and evaporated at reduced pressure. The obtained residue is treated with ethyl acetate

and washed with water. The organic phase is dried with sodium sulphate and evaporated at reduced pressure. The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 9/1. 5 g of the expected compound are obtained as an oil.

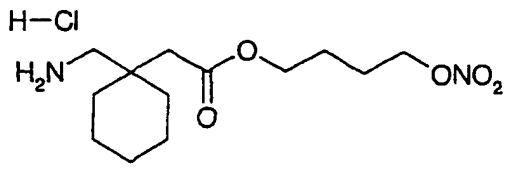
E) Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl] phenyl hydrochloride ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl) cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl ester (5 g, 8.8 mmoles) in ethyl acetate (100 ml), a solution of HCl 1N in ethyl acetate (50 ml) is added. The reaction mixture is left overnight at room temperature, then concentrated under vacuum to a volume of 40 ml. The obtained residue is treated with ethyl ether. The precipitate is filtered and dried under vacuum. 1.8 g of the expected compound are obtained as a white solid having m.p. = 103°-105°C.

^{1}H-NMR ($CDCl_3$) ppm: 8.43 (2H, m); 7.55 (1H, d); 7.10 (3H, m); 6.34 (1H, d); 4.51 (2H, t), 4.26 (2H, t); 3.89 (3H, s); 3.12 (2H, s); 2.81 (2H, s); 1.82 (4H, m); 1.54 (10H, m).

EXAMPLE 2

Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 4-(nitrooxy)butyl hydrochloride ester



A) Synthesis of the 1-(N-tert-butoxycarbonylaminomethyl) cyclohexan acetic acid 4-(bromo)butyl ester

To a solution of 1-(N-tert-butoxycarbonyl aminomethyl)cyclohexan acetic acid (1 g, 3.6 mmoles) in N,N-dimethyl formamide (50 ml) cooled at 0°C, sodium ethylate (246 mg, 3.6 mmoles) is added.

The reaction mixture is left at 0°C under stirring for 30 minutes, and then 1,4-dibromobutane (1.28 ml, 10.8 mmoles) is added. The solution is left under stirring at room temperature overnight, then diluted with ethyl ether and washed with water. The organic phase dried with sodium sulphate is evaporated under vacuum. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 0.7 g of the expected compound are obtained as an oil.

B) Synthesis of the 1-(N-tert-butoxycarbonylaminomethyl) cyclohexan acetic acid 4-(nitrooxy)butyl ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl)cyclohexan acetic acid 4-(bromo)butyl ester (1 g, 2.5 mmoles) in acetonitrile (200 ml) silver nitrate (1.3 g, 7.5 mmoles) is added. The reaction mixture is heated at 80°C for 6 hours sheltered from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 0.8 g of the expected compound are obtained as an oil.

C) Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 4-(nitrooxy)butyl hydrochloride ester

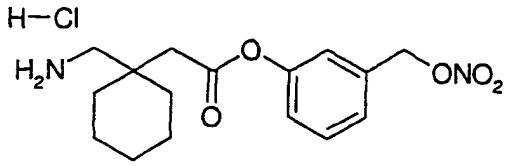
To a solution of 1-(N-tert-butoxycarbonylamino methyl) cyclohexan acetic acid 4-(nitrooxy)butyl ester (0.8 g, 2.06

mmoles) in ethyl acetate (5 ml) a solution of HCl 1N in ethyl acetate (20 ml) is added. The reaction mixture is left for 3 hours at room temperature then it is treated with n-hexane. The precipitate is filtered and dried under vacuum. 0.45 g of the expected compound are obtained as a white solid having m.p. = 80.3°-81.3°C.

^{1}H-NMR (DMSO) ppm: 8.23 (2H, s); 4.58 (2H, t), 4.09 (2H, t); 2.92 (2H, s); 2.56 (2H, s); 1.74 (4H, m); 1.44 (10H, m).

EXAMPLE 3

Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 3-(nitrooxymethyl)phenyl hydrochloride ester (XVI)



A) Synthesis of 3-(bromomethyl)phenol

To a solution of 3-hydroxybenzyl alcohol (4 g, 32.2 mmoles) in methylene chloride (250 ml), cooled at 0°C, tetrabromomethane (12.82 g, 38.6 mmoles) and triphenylphosphine (12.67 g, 48.3 mmoles) are added. The mixture is kept under stirring at 0° for 10 minutes, then evaporated at reduced pressure. The crude product is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 3.5 g of the expected product are obtained.

B) Synthesis of the 1-(N-tert-butoxycarbonylamino-methyl)cyclohexan acetic acid 3-(bromomethyl)phenyl ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl) cyclohexan acetic acid (2.6 g, 9.7 mmoles) in chloroform (200 ml) and N,N-dimethylformamide (2 ml), 4-(bromomethyl)phenol (2g, 10.7 mmoles), dicyclohexylcarbodiimide (4 g, 19.7

mmoles) and N,N-dimethylaminopyridine (24 mg, 0.20 mmoles) are added. The reaction mixture is left at room temperature for 4 hours under stirring, filtered and evaporated at reduced pressure. The obtained residue is treated with ethyl acetate and washed with water. The organic phase is dried with sodium sulphate and evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 9/1. 1.4 g of the compound are obtained as an oil.

C) Synthesis of the 1-(N-tert-butoxycarbonylamino methyl)cyclohexan acetic acid 3-(nitrooxymethyl)phenyl ester

To a solution of 1-(N-tert-butoxycarbonylamino methyl)cyclohexan acetic acid 3-(bromomethyl) phenyl ester (1.4 g, 3.18 mmoles) in acetonitrile (300 ml) silver nitrate (1 g, 6.36 mmoles) is added. The reaction mixture is heated at 50°C for 4 hours sheltered from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 0.75 g of the expected compound are obtained as an oil.

D) Synthesis of the 1-(aminomethyl)cyclohexan acetic acid 3-(nitrooxymethyl)phenyl hydrochloride ester

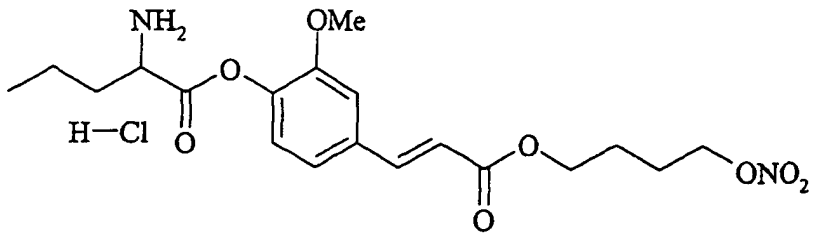
To a solution of 1-(N-tert-butoxycarbonylamino methyl) cyclohexan acetic acid 3-(nitrooxymethyl)phenyl ester (0.75 g, 1.8 mmoles) in ethyl acetate (5 ml), a solution of HCl 1N in ethyl acetate (18 ml) is added. The reaction mixture is left for 15 minutes at room temperature, then it is treated with n-hexane. The precipitate is filtered and dried under

vacuum. 0.45 g of the expected compound are obtained as a white solid having m.p. = 106°-108°C.

^{1}H-NMR (DMSO) ppm: 8.16 (3H, m); 7.52 (1H, t); 7.44 (1H,d); 7.34 (1H, s), 7.28 (1H, d); 5.65 (2H, s), 3.03 (2H, m); 2.86 (2H, s); 1.55 (10H, m).

EXAMPLE 4

Synthesis of the 2-aminopentanoic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester



A) Synthesis of the 1-(N-tert-butoxycarbonylamino) pentanoic acid.

To a solution of 2-aminopentanoic acid (4 g, 34.14 mmoles) in dioxane (40ml) and water (75ml), triethylamine (9.5 ml, 68.29 mmoles) and di-tert-butyldicarbonate (8.94 g, 49.97 mmoles) are added. The reaction mixture is left at room temperature, under stirring for 17 hours. Afte having cooled the solution at 0°C it is brought to pH = 2 with HCl at 5%. One extracts with ethyl acetate, the joined organic phases are washed with water and dried with sodium sulphate.

The solvent is evaporated at reduced pressure to give the compound as an yellow oil which is used without further purification.

B) Synthesis of 2-methoxy-4-[(1E)-3-[4-(bromo)butoxy]-3-oxy-1-propenyl]phenol

To a solution of ferulic acid (11.6 g, 59.7 mmoles) in tetrahydrofuran (400 ml), tetrabromomethane (39.62 g, 119.47 mmoles) and triphenylphosphine (31.34 g, 119.47 mmoles) are added. The obtained mixture is kept under stirring at room temperature for 5 hours, filtered and evaporated at reduced pressure. The obtained crude compound is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 8 g of the expected compound are obtained as a yellow solid having m.p. = 86°-89°C.

C) Synthesis of 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenol

To a solution of 2-methoxy-4-[(1E)-3-[4-(bromo) butoxy]-3-oxy-1-propenyl]phenolo (8 g, 24.3 mmoles) in acetonitrile (500 ml) silver nitrate (12.25 g, 72.9 mmoles) is added. The reaction mixture is heated at 40°C for 12 hours sheltered from light. The formed salt is removed by filtration and the solution is evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 75/25. 4 g of the expected compound are obtained as a yellow solid having m.p. = 65°-68°C.

C) Synthesis of the 2-(N-tert-butoxycarbonylamino) pentanoic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl ester

To a solution of 2-(N-tert-butoxycarbonylamino) pentanoic acid (0.5 g, 2.3 mmoles) in chloroform (12 ml), 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenol (0.86 g, 2.76 mmoles), dicyclohexylcarbodiimide (0.52 g, 2.53 mmoles) and N,N-dimethylaminopyridine (0.03 g, 0.23 mmoles) are added. The reaction mixture is left at room

temperature for 1 hour under stirring, filtered and evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 75/25. 0.5 g of the expected compound are obtained as an oil. Yield 43%.

D) Synthesis of the 2-aminopentanoic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester

To a solution of 2-(N-tert-butoxycarbonylamino) pentanoic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl ester (0.28 g, 0.548 mmoles) in ethyl acetate (7 ml), a solution of HCl in ethyl acetate (6.8 N, 0.700 ml) is added. The reaction mixture is left 3 hours at room temperature. The precipitate is filtered and dried under vacuum. 0.1 g of the expected compound are obtained as a white solid.

^{1}H-NMR (DMSO) ppm: 8.75 (3H, m); 7.62 (1H, d); 7.58 (1H, s); 7.3 (1H, d); 7.2 (1H, d); 6.72 (1H, d); 4.57 (2H, t), 4.26 (1H, t); 4.18 (2H, t); 3.82 (3H, s); 1.95 (2H, m); 1.75 (4H, m); 1.45 (2H, m) 0.98 (3H, m).

CLAIMS

1. Nitrooxyderivative compounds or salts thereof having the general formula (I):

$$A\text{-}(B)_{b0}\text{-}(C)_{c0}\text{-}NO_2 \qquad (I)$$

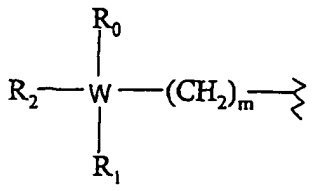
wherein:

c0 is an integer and is 0 or 1, preferably 1;

b0 is an integer and is 0 or 1, with the proviso that c0 and b0 cannot be contemporaneously equal to zero;

A = $R\text{-}T_1\text{-}$, wherein

R is the radical of a precursor drug of formula II:



(II)

wherein:

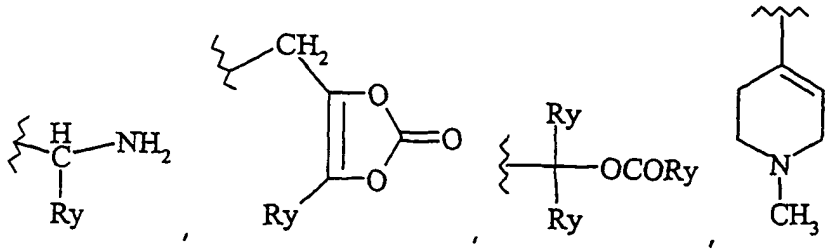
W is a carbon atom or a nitrogen atom;

m is an integer from 0 to 2;

R_0 = H, $-(CH_2)_n\text{-}NHR_{1A}$, n being an integer from 0 to 2, wherein

R_{1A} = H, $-C(O)\text{-}R_{1H}$, $-C(O)O\text{-}R_{1H}$, wherein

R_{1H} is a linear or branched $C_1\text{-}C_{10}$ alkyl, a phenyl or benzyl group; or R_{1H} has one of the following meanings:



(II-B) (II-C) (II-D) (II-E)

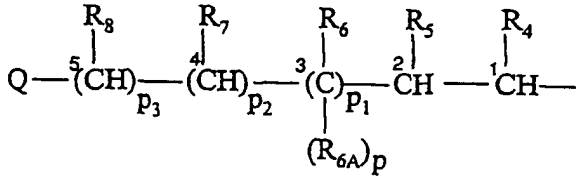
wherein Ry is hydrogen, a linear or branched C_1-C_{10} alkyl, a phenyl or benzyl group;

R_1 = H, when W = N, R_1 is the electronic doublet on the nitrogen atom (free valence);

R_2 is chosen between the following groups:

- phenyl, optionally substituted with an halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;
- *mono- or di-hydroxy* substituted benzyl, preferably 3-4 di-hydroxy substituted;
- amidino group: $H_2N(C=NH)-$;

the radical of formula (IIA), wherein optionally one unsaturation of ethylene type can be present between the carbon atoms in position 1 and 2, or 3 and 4, or 4 and 5:



(IIA)

wherein:

p, p_1, p_2 are integers, equal to or different from each other and are 0 or 1;

p_3 is an integer from 0 to 10;

R_4 is hydrogen, linear or branched C_1-C_6 alkyl, free valence;

R_5 can have the following meanings:

- linear or branched C_1-C_6 alkyl,
- C_3-C_6 cycloalkyl,
- free valence,
- OR_A, wherein R_A has the following meanings:
  - linear or branched C_1-C_6 alkyl optionally substituted with one or more halogen atoms, preferably F,
  - phenyl optionally substituted with one halogen atom or with one of the following groups: $-OCH_3$, $-CF_3$, nitro;

R_6, R_{6A}, R_7, R_8, equal or different, are H, methyl; or free valence;

with the proviso that in the radical of formula (IIA) when one unsaturation of ethylene type is present, between C_1 and C_2, R_4 and R_5 are free valences such as to form the double bond between C_1 and C_2; when the unsaturation is between C_3 and C_4, R_6 and R_7 are free valences such as to form the double bond between C_3 and C_4; when the unsaturation is between C_4 and C_5, R_7 and R_8 are free valences such as to form the double bond between C_4 and C_5;

Q is equal to H, OH, OR_B wherein R_B is benzyl, a linear or branched C_1-C_6 alkyl, optionally substituted with one or more halogen atoms, preferably F, phenyl optionally substituted with one halogen atom or with one of the following groups:

$-OCH_3$, $-CF_3$, nitro; or Q can have one of the following meanings:

- C_3-C_6 cycloalkyl;
- linear or branched C_1-C_6 alkyl;
- guanidine ($H_2NC(=NH)NH-$);
- thioguanidine ($H_2NC(=S)NH-$);

in formula (II) R_2 with R_1 and with W = C taken together form a C_4-C_{10}, preferably C_6, saturated or unsaturated, preferably saturated ring;

T_1 = $(CO)_t$ or $(X)_{t'}$, wherein X = O, S, NR_{1c}, R_{1c} is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1;

B = $-T_B-X_2-T_{BI}-$ wherein

T_B and T_{BI} are equal or different;

T_B= (CO) when t = 0, T_B = X when t' = 0, X being as above;

T_{BI}= $(CO)_{tx}$ or $(X)_{txx}$, wherein tx and txx have the value of 0 or 1; with the proviso that tx = 1 when txx = 0; and tx = 0 when txx = 1; X is as above;

X_2, bivalent radical, is such that the corresponding precursor of B $-T_B-X_2-T_{BI}-$ wherein the free valences of T_B and of T_{BI} are saturated each with OZ, with Z or with $-N(Z^I)(Z^{II})$, being:

Z = H, C_1-C_{10}, preferably C_1-C_5 alkyl linear or branched when possible,

Z^I, Z^{II} equal or different have the values of Z as above, depending on that T_B and/or T_{BI} = CO or X, in function of the values of t, t', tx and txx;

the precursor compound of B as above defined is selected from the following classes of compounds:

- aminoacids, selected from the following: L-carnosine, anserine, selenocysteine, selenomethionine, penicillamine, N-acetyl-penicillamine, cysteine, N-acetylcysteine, glutathione or esters thereof, preferably ethyl or isopropyl ester;
- hydroxyacids, selected from the following: gallic acid, ferulic acid, gentisic acid, citric acid, caffeic, dihydrocaffeic acid, p-cumaric acid, vanillic acid;
- aromatic and heterocyclic polyalcohols, selectd from the following: nordihydroguaiaretic acid, quercetin, catechin, kaempferol, sulphurethyne, ascorbic acid, isoascorbic acid, hydroquinone, gossypol, reductic acid, methoxyhydroquinone, hydroxyhydroquinone, propyl gallate, saccharose, 3,5-di-tertbutyl-4-hydroxybenzylthio glycolate, p-cumaric alcohol, 4-hydroxy-phenylethylalcohol, coniferyl alcohol, allopurinol;
- compounds containing at least one free acid function, selected from the following: 3,3'-thiodipropionic acid, fumaric acid, dihydroxymaleic acid, edetic acid;

C = bivalent radical $-T_c-Y-$ wherein

when b0 = c0 = 1: T_c = (CO) when tx = 0, T_c = X when txx = 0, X being as above defined,

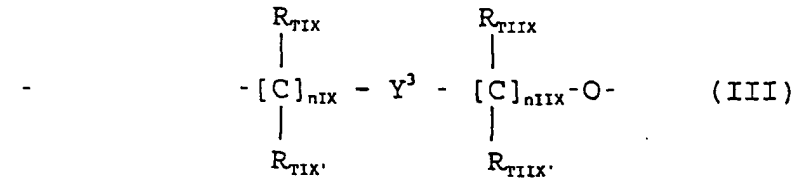
when b0 = 0 : T_c = (CO) when t = 0, T_c = X when t' = 0, X being as above defined,

when c0 = 0 : tx = 0, T_{BI} = X = –O–;

T_c = (CO) when tx = 0, T_c = X when txx = 0, X being as above;

Y has one of the following meanings:

Y_p :



(III)

wherein:

nIX is an integer from 0 to 5, preferably 1;

nIIX is an integer from 1 to 5 preferably 1;

R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other are H or linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H.

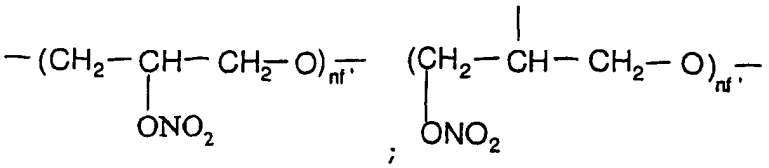
Y^3 is a saturated, unsaturated or aromatic heterocyclic ring, having 5 or 6 atoms, containing from 1 to three heteroatoms, preferably from one to two, said heteroatoms being equal or different and selected from nitrogen, oxygen, sulphur;

or Y can be:

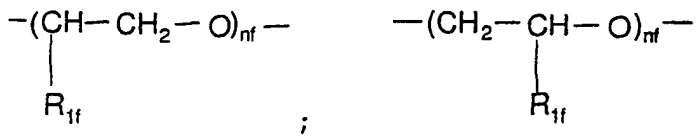
Y_0, selected from the following:

an alkylenoxy group R'O wherein R' is a linear or branched when possible C_1-C_{20}, preferably having from 2 to 6 carbon atoms, or a cycloalkylene having from 5 to 7 carbon atoms, in the cycloalkylene ring one or more carbon atoms can be substituted by heteroatoms, the ring can have side chains of R' type, R' being as above;

or Y is selected from one of the following groups:

- 

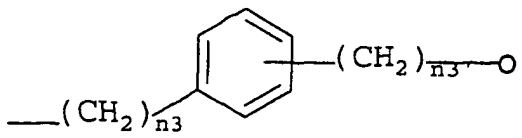
wherein nf' is an integer from 1 to 6 preferably from 1 to 4;

- 

wherein R_{1f} = H, CH_3 and nf is an integer from 1 to 6; preferably from 2 to 4;

Y_{AR}, selected from:

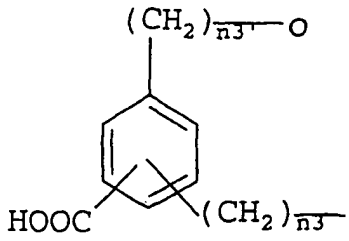
Y_{AR1}:



(V)

wherein n3 is an integer from 0 to 5 and n3' is an integer from 1 to 3; or

Y_{AR2}:



(VI)

wherein n3 and n3' have the above mentioned meaning.

2. Compounds according to claim 1, wherein:

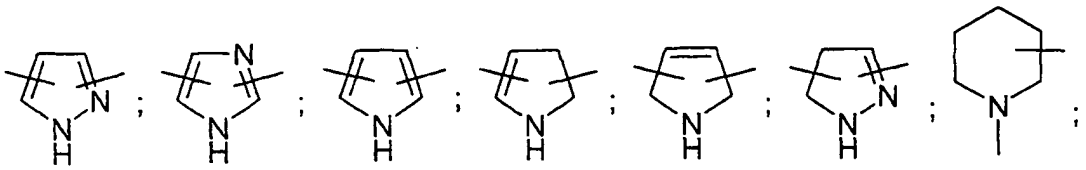
- when in formula (II) W = C, m = 1 and R_0 = $-(CH_2)_n-NH_2$ with n = 1, R_2 and R_1 with W as above form together the cyclohexane ring, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as gabapentine;
- when in formula (II) W = C, m = 0 and R_0 = $-(CH_2)_n-NH_2$ with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q = H, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as norvaline;
- when in formula (II) W = C, m = 0 and R_0 = $-(CH_2)_n-NH_2$ with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the guanidine group, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as arginine;
- when in formula (II) W = C, m = 0 and R_0 = $-(CH_2)_n-NH_2$ with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the thioguanidine group, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as thiocitrulline;
- when in formula (II) W = C, m = 1 and R_0 = $-(CH_2)_n-NH_2$ with n = 1, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 = H, R_5 = Q = CH_3, in the radical A of formula (I) T_1 = CO and the

free valence of A is saturated with OH, the precursor drug of R is known as pregabaline;

- when in formula (II) W = C and it has configuration (S), m = 1 and R_0 = -$(CH_2)_n$-NH_2 with n = 1, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 = H, R_5 = Q = CH_3, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as (S)3-isobutylGABA;
- when in formula (II) W = C, m = 1 and R_0 = R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = 1, p_2 = p_3 = 0, R_4 = R_5 = R_6 = R_{6A} = H, Q is the guanidine group, in the radical A of formula (I) T_1 = NH and the free valence of A is saturated with H, the precursor drug of R is known as agmatine;
- when in formula (II) W = C, m = 2 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical of formula (IIA) wherein p = p_1 = p_2 = p_3 = 0, R_4 and R_5 are free valences and between C_1 and C_2 there is one ethylene unsaturation, Q = H, in the radical A of formula (I) T_1 = CO and the free valence of A is saturated with OH, the precursor drug of R is known as vigabatrine;
- when in formula (II) W = C, m = 0 and R_0 = -$(CH_2)_n$-NH_2 with n = 0, R_1 = H, R_2 is the radical 3-4 di-hydroxy substituted benzyl, T_1 = CO and the free valence of A is saturated with OH, the percursor drug of R is known as 2-amino,(3,4-dihydroxyphenyl)propanoic acid (dopa).

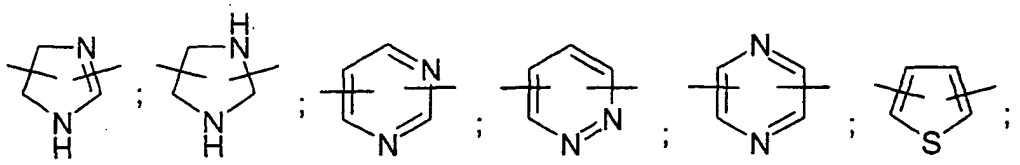
3. Compounds according to claims 1-2, wherein when in formula (I) b0 = 0, Y in the bivalent linking group C is selected between Y_P and Y_{AR} as above defined.

4. Compounds according to claim 3, wherein Y^3 is selected from the following bivalent radicals:

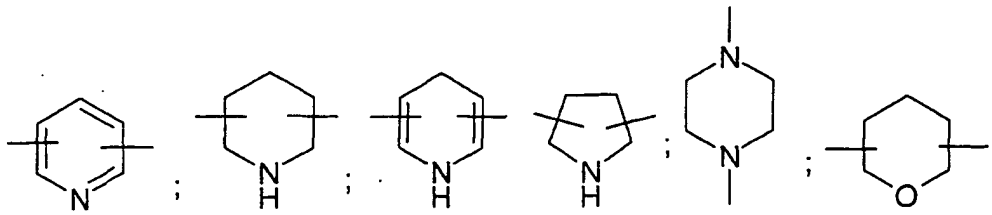


(Y1) (Y2) (Y3) (Y4) (Y5) (Y6)

(Y19)



(Y7) (Y8) (Y9) (Y10) (Y11) (Y18)



(Y12) (Y13) (Y14) (Y15) (Y16) (Y17)

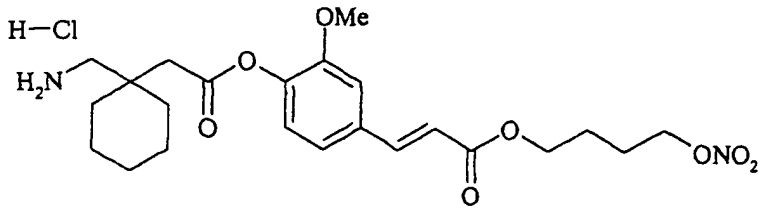
5. Compounds according to claim 4, wherein Y^3 is selected from (Y12), having the two free valences in the ortho position with respect to the nitrogen atom; (Y16) with the two valences linked to the two heteroatoms, Y1 (pyrazol) 3,5-disubstituted; ; (Y19), wherein the free valence on the ring is found in para position to the nitrogen atom.

6. Compounds according to claims 1-5, wherein in formula (I) the precursors of B are the following: ferulic acid, N-

acetylcysteine, cysteine, caffeic acid, hydrocaffeic and gentisic acid.

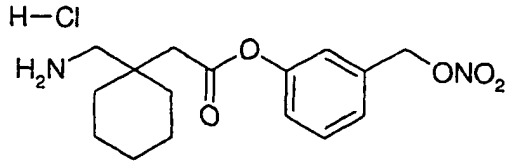
7. Compounds according to claims 1-6, wherein the precursor drugs are selected from gabapentine, norvaline, arginine, pregabaline, (S)3-isobutylGABA, agmatine.

8. Compounds according to claims 1-7, selected from the following: 1-(aminomethyl)cyclohexan acetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy) butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XV)



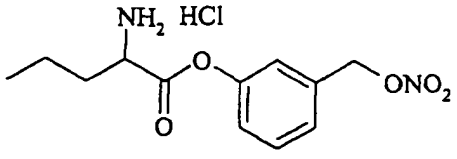
(XV)

1-(aminomethyl)cyclohexan acetic acid 3-(nitrooxymethyl) phenyl hydrochloride ester (XVI)



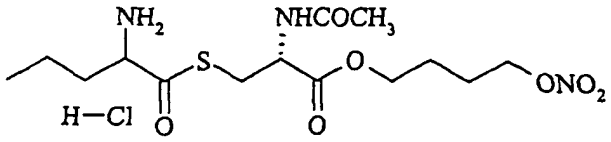
(XVI)

2-aminopentanoic acid 3-(nitrooxymethyl)phenyl hydrochloride ester (XVII)



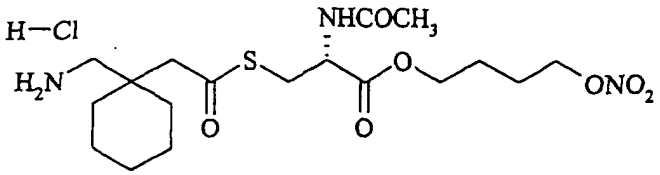
(XVII)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, 2-amino pentanoate hydrochloride (XVIII)



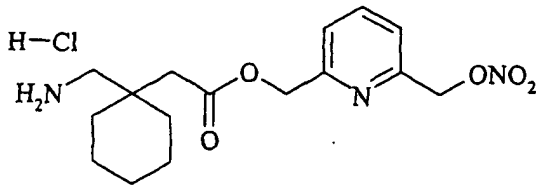
(XVIII)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, 1-(aminomethyl) cyclohexanacetate hydrochloride (XIX)



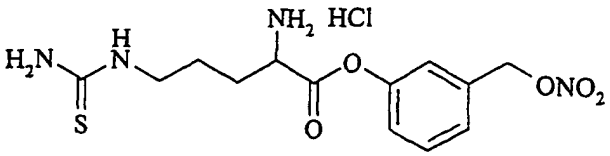
(XIX)

1-(aminomethyl)cyclohexanacetic acid-, [6-(nitrooxy methyl)-2-pyridinyl]methyl hydrochloride ester (XX)



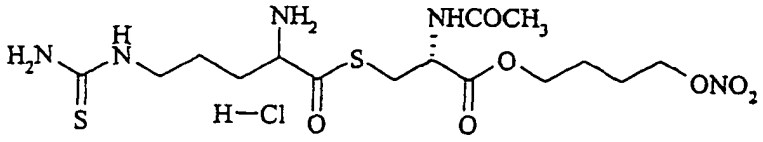
(XX)

alpha-amino-delta-thioureidopentanoic acid, 3-(nitrooxy methyl)phenyl hydrochloride ester (XXI)



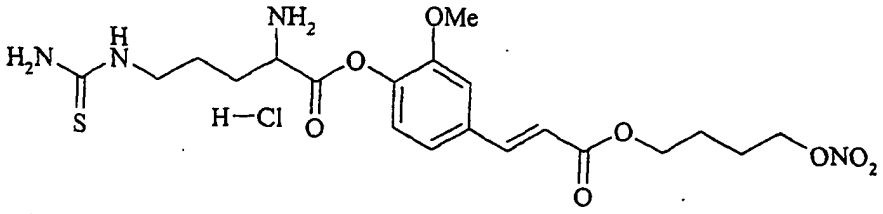
(XXI)

(S)-N-acetylcysteine-, 4-(nitrooxy)butyl ester, alpha-amino-delta-thioureidopentanoate hydrochloride (XXII)



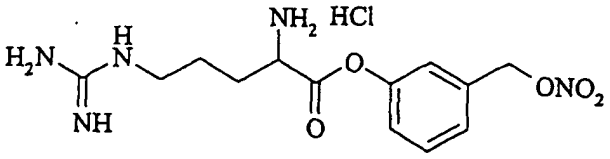
(XXII)

alpha-amino-delta-thioureidopentanoic acid, 2-methoxy-4-[(1E) -3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXIII)



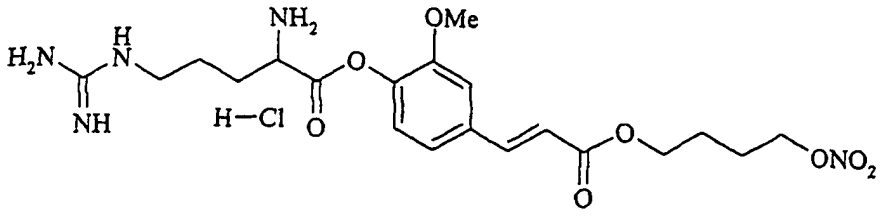
(XXIII)

2-amino-5-guanidinopentanoic acid, 3-(nitrooxy methyl)phenyl hydrochloride ester (XXIV)



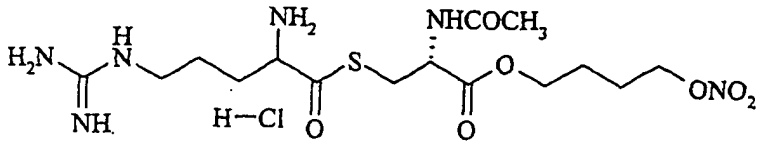
(XXIV)

2-amino-5-guanidinopentanoic acid-, 2-methoxy-4-[(1E) -3-[4-(nitrooxy)butoxy]-3-oxy-1-propenyl]phenyl hydrochloride ester (XXV)



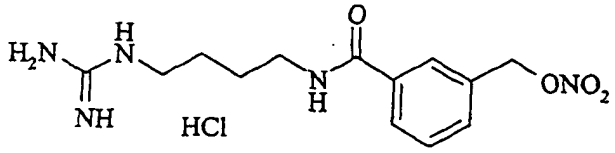
(XXV)

(S)-N-acetylcysteine-4-(nitrooxy)butyl ester, 2-amino-5-guanidinopentanoate hydrochloride (XXVI)



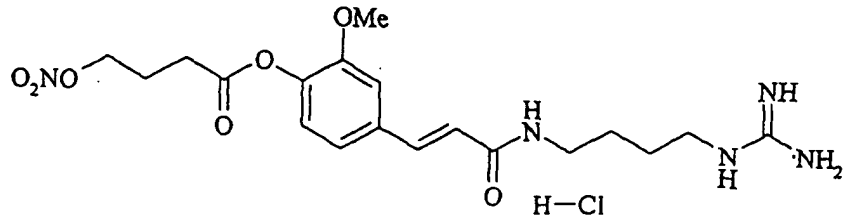
(XXVI)

4-(guanidine)butyl-3-nitrooxymethylbenzamide (XXVII)



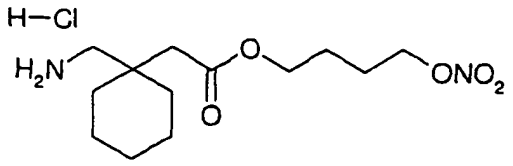
(XXVII)

4-(guanidine)butyl-3-[4-(4'-nitrooxybutyryloxy)-3-(methoxy)] phenyl-2-propenamide chloride (XXVIII)



(XXVIII)

1-(aminomethyl)cyclohexan acetic acid 4-(nitroxy) butyl hydrochloride ester (XXIX)



(XXIX)

9. Compounds according to claims 1-8, as nitrate salts.
10. Compounds according to claims 1-9, in combination with NO donor compounds.
11. Compounds according to claim 10, wherein the NO donor compounds contain in the molecule radicals of drugs belonging to the classes of aspirin, ibuprofen, paracetamol, naproxen, diclofenac, flurbiprofen.
12. Pharmaceutical compositions for parenteral, oral and topical use comprising the compounds according to claims 1-11.
13. Compounds according to claims 1-12, for use as medicament.
14. Use of the compounds according to claims 1-13, for preparing drugs for epilepsy.

INTERNATIONAL SEARCH REPORT

al Application No
PCT/EP 02/06389

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C203/04 C07C229/28 C07C229/08 C07C327/22 C07C335/08
C07D213/30 C07C279/14 C07C279/12 A61K31/195 A61K31/155

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 199614 Derwent Publications Ltd., London, GB; Class B02, AN 1996-136303 XP002213051 & JP 08 027154 A (NIPPON KAYAKU KK), 30 January 1996 (1996-01-30) abstract	1,12-14
X	WO 00 54756 A (UNIV KINGSTON) 21 September 2000 (2000-09-21) page 3, line 27; claims 1,42	1,12-14
X	US 5 883 122 A (BENNETT BRIAN M ET AL) 16 March 1999 (1999-03-16) column 2, line 5; claims 1-13	1,12-14

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 November 2002	03. 12. 02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rufet, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

national Application No
PCT/EP 02/06389

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CA 1 322 958 A (BOLGER GORDON T) 12 October 1993 (1993-10-12) page 1, line 18; claim 1	1,12-14
X	US 5 719 186 A (MUSSO DAVID LEE ET AL) 17 February 1998 (1998-02-17) column 3, line 63; claims 1,2	1,12-14
X	EP 0 372 998 A (BEECHAM GROUP PLC) 13 June 1990 (1990-06-13) abstract; claim 1	1,12-14
X	WO 95 30641 A (NICOX LTD ;DEL SOLDATO PIERO (IT); SANNICOLO FRANCESCO (IT)) 16 November 1995 (1995-11-16) claim 1	1,12
X	WO 95 09831 A (NICOX LTD ;DEL SOLDATO PIERO (IT)) 13 April 1995 (1995-04-13) cited in the application abstract; claim 1	1,12
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C.(Continuation) D CUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	KAWASHIMA ET AL: "Synthesis and Pharmacological Evaluation of (Nitrooxy)alkyl Apovincaminates" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 36, 1993, pages 815-819, XP002210204 ISSN: 0022-2623 page 819, column 1; table 1	1,12
X	CIRINO G ET AL: "INHIBITION OF INDUCIBLE NITRIC OXIDE SYNTHASE EXPRESSION BY NOVEL NONSTEROIDAL ANTI-INFLAMMATORY DERIVATIVES WITH GASTROINTESTINAL SPARING PROPERTIES" BRITISH JOURNAL OF PHARMACOLOGY, BASINGSTOKE, HANTS, GB, vol. 117, no. 7, April 1996 (1996-04), pages 1421-1426, XP000938504 ISSN: 0007-1188 abstract	1,12
X	OGAWA T ET AL: "SYNTHESIS AND ANTIHYPERTENSIVE ACTIVITIES OF NEW 1,4-DIHYDROPYRIDINE DERIVATIVES CONTAINING NITROOXYALKYLESTER MOIETIES AT THE 3- AND 5-POSITIONS" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 6, no. 41, June 1993 (1993-06), pages 1049-1054, XP001093850 ISSN: 0009-2363 page 1054, column 1, paragraph 2; tables I-III	1,12
A	WO 00 44705 A (NICOX SA ;DEL SOLDATO PIERO (IT); GARUFI MICHELE (IT)) 3 August 2000 (2000-08-03) abstract; example 1	8
A	WO 98 42661 A (YISSUM RES DEV CO ;HAJ YEHIA ABDULLAH (IL)) 1 October 1998 (1998-10-01) claims 1-10	8
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B x I Observations wher certain claims were f und unsearchable (C ntinuation of it m 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-7,9-14
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT, no additional fees are to be refunded.

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-14 partially

   compounds having the following common structural feature: -(CH2)3-ONO2 useful for preparing drugs for epilepsy

2. Claims: 1-14 partially

   compounds having the following common structural feature: phenyl-CH2-ONO2 substituted in meta position, useful for preparing drugs for epilepsy

3. Claims: 1-14 partially

   compounds having the following common structural feature: 2-NO2-O-CH2-pyridyl which is substituted in the 6 position with the group -CH2-O-(CO)-, useful for preparing drugs for epilepsy

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-7,9-14

Present claims 1-7, 9-14 relate to an extremely large number of possible compounds/uses. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claim 8 and of the examples 1-4.

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty, only a few of them have been cited in the search report. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claims is impossible. Consequently, the search has been restricted to the compounds of claim 8 and of the examples 1-4 as abovementioned.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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